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Atty. Docket No. TAK03 P-323

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November 9, 2005
Date

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Art Unit	:	1651
Examiner	:	Francisco C. Prats
Appln. No.	:	10/018,770
Applicants	:	Yoshihito Ikeda et al.
Filing Date	:	December 17, 2001
Confirmation No.	:	2012
For	:	DRUG COMPOSITION CONTAINING A LECITHIN-MODIFIED SUPEROXIDE DISMUTASE

Mail Stop Appeal Brief - Patents
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Alexandria, Virginia 22313-1450

SUPPLEMENTAL APPEAL BRIEF (37 CFR §41.37)

This amended brief is in furtherance of the Appeal Brief filed in this case on September 7, 2005, and the Notification of Non-Compliant Appeal Brief mailed October 13, 2005.

The fees required under §41.20(b)(2) have already been submitted and not additional fees are due. However, if there is any fee due in connection with the filing of this document, please charge the fee to our Deposit Account No. 16-2463.

This brief has been amended to comply with the Examiner's refusal to consider a published document (Lindberg et al., "Folding of human superoxide dismutase: Disulfide reduction prevents dimerization and produces marginally stable monomers," *Proceedings of the National Academy of Sciences of the United States of America*, November 9, 2004, Vol. 101, No. 45) showing that those of ordinary skill in the art would have recognized that there is a distinction between stabilization of SOD against dimerization and stabilization of SOD against

denaturation, and that the use of sucrose to prevent denaturation of dimerized SOD would actually facilitate denaturation.

This brief contains these items under the following headings, and in the order set forth below (37 CFR §41.37(c)):

I. Real Party in Interest

II. Related Appeals and Interferences

III. Status of Claims

IV. Status of Amendments

V. Summary of Claimed Subject Matter

VI. Grounds of Rejection to Be Reviewed on Appeal

VII. Argument

VIII. Conclusion

Appendix of Claims Involved in the Appeal

Evidence Appendix

Related Proceedings Appendix

The final page of this brief bears the attorney's signature.

I. Real Party in Interest

The real party in interest in this application is LTT Bio-Pharma Co., Ltd., the assignment to which was recorded at Reel 014723, Frame 0283.

II. Related Appeals and Interferences

There are not any related appeals or interferences which will directly affect, or be directly affected by, or having a bearing on, the Decision of the Board of Patent Appeals and Interferences.

III. Status of Claims

This is an appeal from the rejection of claims 1, 4, 6-8, 10-14 and 19. Claims 2, 3, 5, 9 and 15-18 have been canceled. No claims have been allowed or withdrawn from consideration.

IV. Status of Amendments

There have not been any amendments filed after the Final Rejection being appealed.

V. Summary of Claimed Subject Matter

Independent claim 1 is directed to a drug composition comprising sucrose and a lecithin-modified superoxide dismutase. Details regarding the meaning of a lecithin-modified superoxide dismutase (also known as phosphatidylcholine-modified superoxide dismutase or PC-SOD) are provided at page 3, lines 1-12 of the specification, and from page 6, line 4 through page 11, line 5 of the specification.

VI. Grounds of Rejection to Be Reviewed on Appeal

Claims 1, 4, 6-8, 10-14 and 19 stand rejected under 35 U.S.C. §103(a) as being unpatentable over JP 9-117279 in view of JP-304882.

VII. Argument

The claims encompass a drug composition comprising a lecithin-modified superoxide dismutase (also referred to as phosphatidylcholine-modified superoxide dismutase or PC-SOD) and sucrose.

The JP '279 document is relevant only to the extent that it discloses PC-SOD, and its potential uses and advantages in pharmacological therapeutic treatments. The JP '279 document does not teach or suggest a need for stabilizing PC-SOD, thus suggesting that PC-SOD does not require stabilization.

The JP '882 translation makes numerous and unambiguous references to the use of stabilizing agents for preventing dimerization of SOD (not PC-SOD). For example, at page 3, the JP '882 translation reads as follows:

> No decrease in the enzymatic action of human SOD is observed when this protein is subjected to freezing and thawing or freeze-drying processes, nor is formation of insoluble matter visible to the naked eye. However, human SOD subjected to analysis by sodium dodecyl sulfate - polyacrylamide

> electrophoresis, high-performance gel filtration liquid chromatography, and the like produces by-products consisting mostly of dimers.
>
> Thus, the use of human SOD in pharmaceutical products necessitates its stable storage. However, by-products resulting from the storage process may have allergenic side effects; the generation of such substances must be prevented.

This clearly indicates that the authors did not observe any loss of activity, such as may be attributable to denaturation, but observed the formation of dimers, which apparently are only undesirable because they are believed to have an allergenic side effect.

Consistent with the above-quoted statements are the results set forth in Tables 1 and 2 (pages 11 and 17, respectively) which show an absence of denaturation during as many as 10 freeze-thaw cycles of an SOD-containing composition, regardless of whether the composition contained a stabilizer (sorbitol, inositol, sucrose, trehalose or maltose), or no stabilizer at all (Comparative Example 1). However, the results of Table 1 show that while the stabilizers did not affect denaturation, they provided some reduction in the amount of 79 KD material observed, which the authors regarded as a dimer of SOD. Similarly, the results shown in Table 2 indicate that sorbitol (Embodiment 6), mannitol (Embodiment 7), inositol (Embodiment 8), sucrose (Embodiment 9), trehalose (Embodiment 10), maltose (Embodiment 11), lactose (Embodiment 12), and fructose (Embodiment 13) reduce the amount of 79 KD SOD material formed during freeze-drying of SOD as compared with a similar composition that does not contain a stabilizer (Comparative Example 2). Each of these stabilizers reduces 79 KD product formation, without causing denaturation. In contrast, Comparative Examples 3-5 show that arabinose, glucose and galactose, while also reducing the formation of 79 KD SOD product, cause denaturation. Tables 1 and 2 from the JP '882 translation indicate that denaturation of human SOD does not occur during repeated (up to 10 cycles) freezing and thawing or freeze-drying, except possibly when certain stabilizers outside the scope of the invention disclosed therein (e.g., arabinose, glucose and galactose) are employed. There is some apparent ambiguity on this issue, since the description of the Comparative Examples 3-5 each state "DEAE analysis did not reveal any denaturation of human SOD." However, these statements are inconsistent with the tables, and

are also inconsistent with the statement at page 4, second full paragraph of the JP '882 translation which reads as follows:

> However, even with the combination of aldose monosaccharides such as galactose, arabinose, glucose, and the like to human SOD prior to freeze-drying, analysis by anion-exchange chromatography reveals denaturation (Comparative Example 3). Thus, the use of aldose monosaccharides to prevent denaturation of human SOD during freezing or freeze-drying is undesirable.

The results listed under "Test Method (3) Denaturation" in Tables 1 and 2 were determined by anion-exchange chromatography (see page 8, second full paragraph, which indicates that analysis by anion-exchange chromatography is referred to as DEAE analysis). Thus, the above-quoted language clearly refers to Comparative Examples 3-5. When properly understood with reference to the disclosure in its entirety, the tabulated data suggest that denaturation of human SOD does not occur unless a material which causes denaturation is added. Clearly, the JP '882 translation is teaching that lactose, arabinose and glucose cause denaturation of human SOD, which would not otherwise occur during freezing or freeze-drying.

The Examiner has taken the position that "the use of sucrose as a protein stabilizing agent for PC-SOD is considered obvious, in view of the art-recognized stabilizing effect of sucrose on proteins, including SOD, in storage processes using lyophilization (i.e., freeze-drying)."

The sole issue in this application can be resolved by determining whether a prior art disclosure to add sucrose to SOD for preventing or reducing denaturation (unfolding of the SOD) and/or dimerization (alleged by the prior art to have allergenic side effects) would motivate one having ordinary skill in the art to add sucrose to phosphatidylcholine-modified SOD (PC-SOD).

There is an absence of any suggestion in the prior art that PC-SOD is susceptible to denaturation, that dimerization of PC-SOD is undesirable, or that PC-SOD dimers have allergenic side effects. To the contrary, U.S. Patent No. 5,762,929 (Exhibit 1) discloses that PC-SOD is "useful as an anti-inflammatory agent without adverse effect such as antigenicity" (column 1, lines 59-61). This means that PC-SOD does not exhibit allergenic side effects,

although it already "is a homodimer" (see column 7, line 38 of U.S. Patent No. 5,762,929 (Exhibit 1)). Thus, the motivation disclosed in the JP '882 translation for adding a stabilizer such as sucrose to SOD is not present with PC-SOD.

While the JP '882 translation indicates that bovine SOD (not PC-SOD) is susceptible to denaturation during freeze-drying, those having ordinary skill in the art would not expect PC-SOD to undergo denaturation during freeze-drying, and may actually expect that the addition of sucrose could cause denaturation. There is an equilibrium relationship between denaturated (uncoiled) SOD monomer (D) and the folded monomers (M), and another equilibrium relationship between the folded monomers (M) and the SOD dimer (M_2). Denaturation of SOD dimers cannot occur unless each of the individual dimers is first dissociated into two folded monomers (M). The JP '882 translation suggests that sucrose prevents dimerization of SOD, which necessarily suggests that the addition of sucrose to SOD will drive the kinetics toward dissociation of dimers (M_2) into folded monomers (M) that can subsequently be converted to denatured monomers (D). Thus, one skilled in the art would not be motivated to add sucrose to PC-SOD, since therapeutically active PC-SOD is a homodimer (a molecule comprised of two identical polypeptide chains) that does not exhibit antigenicity, and because denaturation of SOD dimers cannot occur unless the SOD is first dissociated into monomers.

It should be noted that U.S. Patent No. 5,762,929 (Exhibit 1) discloses (Example 2, column 11, line 46 through column 12, line 3) tablets and capsules prepared with lyophilized PC-SOD, without suggesting that there is any need for adding a stabilizer of any type during freeze-drying of the PC-SOD (lactose is added to the tablet as an excipient along with the already lyophilized PC-SOD). The application for U.S. Patent No. 5,762,929 (Exhibit 1) was based on a Japanese application filed January 31, 1995, well after the August 12, 1989 publication date of the JP '882 application. This strongly suggests that while there have been well known stability issues with SOD, there are no similar stability issues with PC-SOD that would suggest utilization of stabilizers.

Those having ordinary skill in the art of preparing pharmaceutical compositions for the treatment of disease are typically very well educated and possess a comprehensive knowledge of

organic chemistry and biochemistry. A person of ordinary skill in the pertinent art would typically have an advanced degree in chemistry, molecular biology and/or pharmacology, would be fully cognizant of the technology described in the prior art, and would be capable of understanding the underlying chemistry. Thus, a person of ordinary skill in the art would understand that lecithin-modified superoxide dismutase (PC-SOD) is a chemical substance that is different from SOD. It is well known that PC-SOD differs significantly from conventional SOD with respect to distribution within the living body and affinity to self. It is also well known that PC-SOD retains an extremely uniform activity as compared with SOD, so that it is expected to enhance the pharmacological activity of SOD, reduce side effects, and promote absorption.

Because it is well known that PC-SOD is chemically very differently from SOD, those having ordinary skill in the art would not expect sucrose to have the same stabilizing effect on PC-SOD as it does on SOD. In fact, it would be contrary to the teachings of the prior art to shift the kinetics and equilibrium toward monomeric PC-SOD and one step closer to denatured (uncoiled) PC-SOD (assuming, as the Examiner has, that PC-SOD and SOD exhibit similar chemical properties).

It is respectfully submitted that the rejection is not supported by the prior art, but is instead based on speculation and hindsight. It is based on speculation that those having ordinary skill in the art would expect allergenic side effects due to dimerization of PC-SOD, similar to the alleged problems associated with dimerization of SOD, despite the fact that the prior art (Exhibit 1) teaches that therapeutically active PC-SOD already exists as a dimer and does not exhibit allergenic side effects. It is further based on speculation that PC-SOD would be expected to undergo denaturation during freeze-drying, despite the fact that the prior art teaches that PC-SOD is not susceptible to denaturation, and only discloses denaturation during freeze-drying of bovine SOD, not PC-SOD or human SOD, with PC-SOD being at least as different chemically from SOD as bovine SOD is from human SOD (e.g., according to the JP '882 translation, bovine SOD is susceptible to denaturation during freeze-drying, whereas human SOD is not). There is no reasonable basis for concluding from the prior art that there is a need

for adding a stabilizer such as sucrose to protect PC-SOD against degradation of any type. In fact, sucrose would be expected to bring the PC-SOD dimer one step closer to denaturation.

Appellants have discovered that there is a loss of biological activity of PC-SOD during freeze-drying and/or freeze-thaw cycles due only to degradation of the phosphatidylcholine (PC) moieties. Appellants discovered this problem and a solution to this problem without any guidance from the prior art. It is only by utilizing Appellants' own teachings as a guide that one of ordinary skill in the art could misinterpret the teachings of the prior art to piece together Appellants' invention.

VIII. Conclusion

Upon consideration of the applied prior art references and applicable law, Appellants submit that reversal of the rejection is appropriate and is requested.

Respectfully submitted,

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Date

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Appendix of Claims (35 USC §41.37(c)

1. A drug composition comprising sucrose and a lecithin-modified superoxide dismutase represented by the following general formula (I):

$$SOD'(Q\text{-}B)_m \qquad (I)$$

wherein SOD' is a residue of superoxide dismutase; Q is a chemical crosslinking; B is a residue without a hydrogen atom of a hydroxyl group of lysolecithin having the hydroxyl group at the 2-postion of glycerol; m is an average number of bonds of lysolecithin to one molecule of superoxide dismutase which is a positive number of 1 of more.

4. The drug composition according to claim 1 wherein a fatty acid content in the drug composition is 0.13-0.15 μmol/mg protein.

6. The drug composition according to claim 1 or 4 wherein Q is
$-C(O)-(CH_2)_n-C(O)-$, n being an integer of 2 or more.

7. The drug composition according to claim 1 or 4 wherein SOD' is a residue of human superoxide dismutase.

8. The drug composition according to claim 1 or 4 wherein SOD' is a residue of a modified form of superoxide dismutase in which an amino acid in 111-position of an amino acid sequence of human superoxide dismutase is converted into S-(2-hydroxyethylthio) cysteine.

10. The drug composition according to claim 1 or 4 wherein n is an integer of 2 to 10.

11. The drug composition according to claim 1 or 4 wherein m is a positive number of 1 to 12.

12. The drug composition according to claim 1 or 4 wherein the sucrose has been treated with activated charcoal.

13. The drug composition according to claim 1 or 4 wherein the drug composition is lypholized.

14. The drug composition according to claim 1 or 4 wherein a weight ratio of the lecithin-modified superoxide dismutase to sucrose is 0.4/100-60/100.

19. A composition containing lecithin-modified superoxide dismutase that is reconstituteable from a dry form and which has been stabilized against degradation due to cleavage within the lecithin moieties, comprising:

lyophilized lecithin-modified superoxide dismutase; and

sucrose in an amount that is effective to stabilize the lecithin-modified superoxide dismutase against degradation due to cleavage within the lecithin, whereby there is not any observable difference in the amount of degradation products before lyophilization and after re-dissolution, and wherein the composition completely dissolves in water in less than 10 seconds.

Evidence Appendix (35 USC §41.37(c))

The following evidence submitted during prosecution of this application are relied upon by Appellants in this appeal:

Exhibit 1: U.S. Patent No. 5,762,929

Related Proceedings Appendix (35 USC §41.37(c))

There have not been any related appeals or interferences during pendency of this application.